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Evidence of graft-versus-tumour effect following allogeneic haematopoietic stem cell transplantation in renal cancer other than clear cell type

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Several studies have demonstrated that allogeneic haematopoietic stem cell transplantation has potent antitumour effect not only against haematological but also against solid malignancies.[1] Main evidence of the potency of GVT effect is represented by sustained remissions obtained after NST in patients with metastatic renal cell carcinoma (RCC) refractory to conventional cytokine-based immunotherapy.[2,3] This evidence supports the notion that RCC harbours immunogenic peculiarities[4–6] that render this tumour responsive to immunotherapies.[7] Interestingly, only clear cell carcinoma, but not other RCC histotypes, has been reported to respond to NST.[2,8,9] Whether this is due to the small number of patients receiving NST for RCC other than those of the clear cell type or due to a real resistance of other histotypes remains to be defined. We have observed objective tumour response following NST in a patient with metastatic papillary RCC.

A 56 year-old male underwent right nephrectomy for stage II (AJCC criteria-VI Ed.) papillary renal carcinoma. After 5 years in June 2002, he relapsed in lungs, and left laterocervical as well as mediastinal lymph nodes. Biopsy of laterocervical lymph node confirmed the diagnosis of metastatic papillary renal carcinoma. From July 2002 to October 2002, he received treatment with 5-fluorouracil, interleukin-2 and α-interferon with progression of disease. In January 2003, after signing informed consent, he received NST from his 72 year-old HLA-identical brother according to the European Blood and Marrow Transplantation (EBMT) phase I NST protocol for refractory solid tumours, approved by the Ethical Committee of Ospedale Niguarda Ca' Granda.

Pretransplant conditioning regimen consisted of i.v. cyclophosphamide 60 mg/kg once daily on days −3 and −2 and i.v. fludarabine 30 mg/m^2 once daily from day −7 to −3. On day 0, a total of 2.2×10^6 CD34+ and 3.2×10^8 CD3+ donor cells/kg (recipient body weight) were transplanted into the patient. Donor cells were previously collected from the 72 year-old HLA-identical brother by blood leukapheresis following administration of Filgrastim 300 μg subcutaneously twice a day for 6 consecutive days. Immunosuppression for GVHD prophylaxis consisted of cyclosporin and short-course methotrexate. Antimicrobial therapy followed institutional protocols consisting of itraconazole for antifungal prophylaxis, acyclovir for antiviral prophylaxis and ciprofloxacin for antibacterial prophylaxis. The degree of donor–recipient chimerism in both myeloid and T-cell lineages was assessed by PCR assay of minisatellite regions.

Engraftment was achieved on day +12 and early post-transplant course was uneventful. Cyclosporin administration was tapered and discontinued on day +120, in the absence of GVHD and with 60% T-cell donor chimerism. Clinical evaluation by physical examination and CT scan performed on days +60 and +120 (Figure 1a and b)

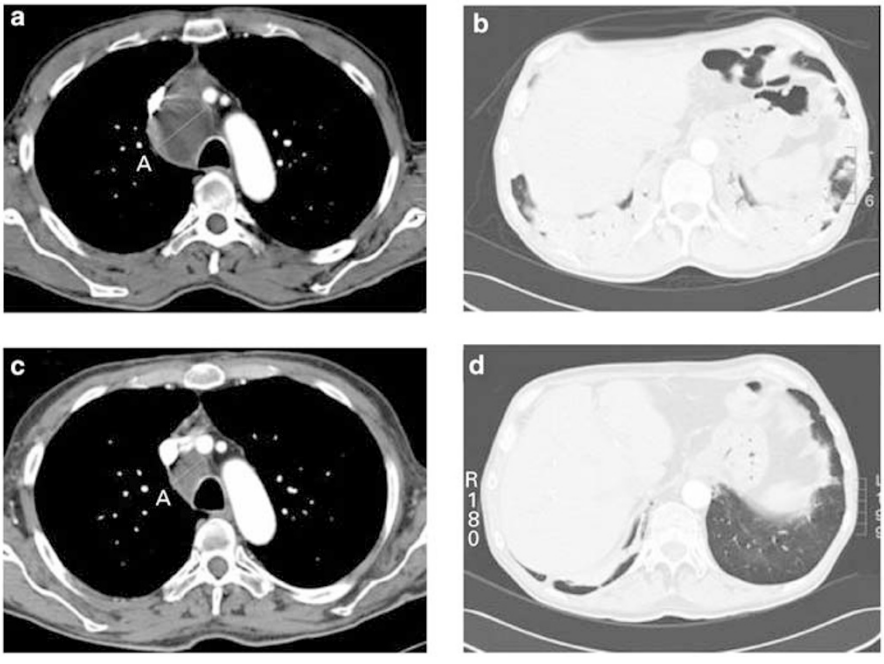

Figure 1 CT scan of patient at day +120 (**a**, **b**) and +190 after allogeneic transplantation (**c**, **d**).

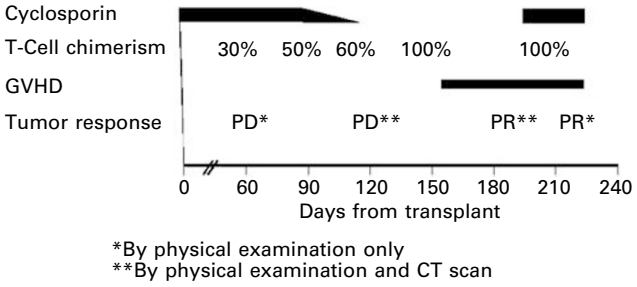

Figure 2 Relevant clinical and biological parameters of patient following allogeneic transplantation.

showed a marked disease progression as compared to baseline. Full donor T-cell chimerism was obtained on day +150 (Figure 2) along with the appearance of grade 1 cutaneous GVHD, which did not require treatment. On day +190, objective tumour regression >50% was documented by CT scan (>50% reduction of mediastinal and lung metastases – Figure 1c and d) and by physical examination (>50% response up to limits of physical detection of laterocervical nodes). At 1 week after evidence of tumour response, the patient developed hepatic and extensive mucocutaneous GVHD. Cyclosporine was reinstituted along with steroids and subsequently mycophenolate. Despite this therapy, hepatic GVHD progressed to liver failure, and the patient died on day +223 still with sustained tumour response (Figure 2).

In the present case, regression of papillary RCC following NST can be attributed to an immune-mediated effect. In fact, tumour progressed in the early post-transplant phase, thus indicating that the conditioning regimen did not affect the course of the disease. In addition, the clinical response associated with onset of GVHD and the achievement of full donor chimerism represents indirect evidence of a GVT effect. This is the first demonstration that NST can generate a meaningful GVT effect in RCC other than clear cell type. Therefore, this therapeutic approach should be considered also in less common histologies of RCC. However, the case reported here underlines that NST approach, while carrying a high risk of life-threatening complications, should be proposed only within controlled trials and when conventional treatments have failed.

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